THE LANCET

Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sacco C, Del Manso M, Mateo-Urdiales A, et al. Effectiveness of BNT162b2 vaccine against SARS-CoV-2 infection and severe COVID-19 in children aged 5–11 years in Italy: a retrospective analysis of January–April, 2022. *Lancet* 2022; published online June 30. https://doi.org/10.1016/S0140-6736(22)01185-0.

Supplementary materials to the article:

Effectiveness of BNT162b2 vaccine against SARS-CoV-2 infection and severe COVID-19 in children 5–11 years old in Italy: a retrospective analysis of January–April, 2022

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Supplementary Material 1: Sensitivity analysis

A sensitivity analysis was done to assess the robustness of our results with respect to the exclusion criteria used to define the study population.
We estimated IRRs of SARS-CoV-2 infections and severe COVID-19, all the 599 169 notified infections that preceded vaccination were included in the analysis (**Model 1**). We then estimated vaccine effectiveness excluding people with SARS-CoV-2 infection diagnosed in the previous 90 days (**Model 2**).
Finally, we did another sensitivity analysis estimating vaccine effectiveness on the vaccinated population alone (**Model 3**), using the exposure interval of 4‑10 days from the first dose of vaccine as a reference and including the frailty status (healthy, immunocompromised, or affected by a chronic pathology) as an additional covariate.

Table S1. COVID-19 BNT162b2 vaccine effectiveness against laboratory-confirmed COVID-19–related with diagnosis among children aged 5–11 years

Model	Vaccination status	VE (%)	95% CI	
Model 1	Partially vaccinated	29·5	28·5·	30·4·
	Fully vaccinated	30·4	29·5·	31·3·
Model 2	Partially vaccinated	31·9	30·9·	32·8·
	Fully vaccinated	33·0	32·1·	33·9·
Model 3	Partially vaccinated	24·3	20·6	27·8·
	Fully vaccinated	21·8	16·1	27·2·

Table S2. COVID-19 BNT162b2 vaccine effectiveness against severe COVID-19 among children aged 5–11 years

Model	Vaccination status	VE (%)	95% CI	
Model 1	Partially vaccinated	37·0	19·5·	50·7·
	Fully vaccinated	39·9	20·6·	54·6·
Model 2	Partially vaccinated	38·1	20·9·	51·5·
	Fully vaccinated	41·1	22·2·	55·4·
Model 3	Partially vaccinated	39·4	3·8·	61·9·
	Fully vaccinated	44·1	9·0	65·7

Table S3. Effectiveness of BNT162b2 vaccines against laboratory-confirmed COVID-19–related with diagnosis at different time intervals after completion of the primary vaccination cycle

	Model 1			Model 2			Model 3		
Vaccination status	VE (%)	95% CI		VE (%)	95% CI		VE (%)	95% CI	
Partially vaccinated	29·5	28·5·	30·4·	31·9	30·9·	32·8·	23·9	20·4	27·3
0-14 days fully vaccinated	39·5	38·5·	40·5·	41·4	40·4·	42·4·	33·3	28·2	37·9
15-28 days fully vaccinated	30·2	29·0	31·4·	32·3	31·1·	33·5·	22·0	14·9	28·5
29-42 days fully vaccinated	23·9	22·5·	25·3·	26·4	25·0·	27·7·	14·0	6·6	20·7
43-84 days fully vaccinated	21·9	20·4·	23·4·	24·7	23·2·	26·2·	6·8	1·3	12·0

Supplementary Material 2: Conditions defining the frailty status

Conditions defining comorbidities giving priority access to vaccination

Description
Respiratory diseases requiring oxygen therapy, idiopathic pulmonary fibrosis
Advanced heart failure (Classes III-IV NYHA) and post cardiogenic shock patients
Amyotrophic lateral sclerosis and other motor neuron disorders, multiple sclerosis, muscular dystrophy, infantile cerebral palsy, myasthenia gravis, dysimmune neuropathies
Type 1 diabetes, Type 2 diabetes with complications or requiring combination therapy (with at least two antidiabetes drugs)
Addison's disease
Panhypopituitarism
Cystic fibrosis
Cirrhosis of the liver
Intracerebral ischemic or hemorrhagic event that has led to impaired neurological and cognitive
Individuals who have suffered a stroke in 2020 - 2021, or who have had a stroke prior to 2020 ranked as level 3 or higher
Thalassemia major
Sickle cell anemia
Other severe anemias
Down syndrome
Body Mass Index >35
Severely disabled persons pursuant to law 104/1992 art. 3 paragraph 3

Conditions defining immunocompromise

ICD9-CM	Description
279.8	Defects of the complement system. Other specified disorders involving the immune mechanism; Deficiency or dysfunction of a single component (C1-C9)
279.1	Deficiency of cell-mediated immunity
279.0	Deficiency of humoral immunity
042, 079.53, V08	Human immunodeficiency virus [HIV] disease, Human immunodeficiency virus, type 2 [HIV-2], Asymptomatic human immunodeficiency virus [HIV] infection status
279	Disorders involving the immune mechanism
	Congenital and acquired disorders with poor antibody production, drug-induced immunosuppression

Supplementary Material 3: RECORD statement

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract under "Methods". Title and abstract under "Methods" In abstract under "Methods"
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Page 4 under "Introduction"
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 4 under "Introduction"
Methods					
Study Design	4	Present key elements of study design early in the paper			Page 4 under "Methods-Data source and population"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Page 5 under "Methods-Outcome definition and study period"
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.	Page 4 and 5 under "Methods-Data source and population" Not relevant. We included all the population in the age group under study. Exclusions are clearly explained in methods and Figure 1

		number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Flowdiagram as Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	We explain the outcomes measured, its definition and the covariates in Pages 5 and 6. Under "Methods – Statistical analysis"
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			We explain the sources of data of each variable in Pages 4 Under "Methods – Data source and population" and "Methods –Statistical analysis" (first paragraph)
Bias	9	Describe any efforts to address potential sources of bias			In pages 5 and 6 under "Methods – Statistical analysis" (first paragraph)
Study size	10	Explain how the study size was arrived at			Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			In page 5 under "Methods – Statistical analysis" (first paragraph)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			In pages 5 and 6 under "Methods – Statistical analysis"
Data access and		..		RECORD 12.1: Authors should describe the extent to which the investigators had	In page 2, under

cleaning methods				access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	"Methods – Data source and population" we explain that the databases are held by the National Public Health Institute and the Ministry of Health. These are the affiliations of the authors. In page 4, under "Methods – Data source and population" we explain how we have cleaned records by excluding inconsistent data. More detail in Figure 1
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	In page 4, under "Methods – Data source and population" we explain the linkage we did and the methods used
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	In pages 6 and 7, under "Results" we describe the selection of persons and the exclusions for each reason. We also include a flow diagram in Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time			In pages 6 and 7 under "Results", we describe the characteristics of the study participants (see Table 1)

		(*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			In page 7, under "Results" (third paragraph)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			In page 7, under "Results" (fourth paragraph)
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			In page 7, under "Results" (last paragraph)
Discussion					
Key results	18	Summarise key results with reference to study objectives			In page 8, under "Discussion" (first two paragraphs)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	In page 9, under "Discussion – Strengths and limitations" we specify limitations related to the data, and possible confounding factors/bias related to the study
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			In pages 8 and 9, under "Discussion"
Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Not applicable as the authors received no financial support for the research
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Not relevant as we did not publish the study protocol and privacy issues prevent us to publish any data used.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Supplementary Material 4. Breakdown of severe COVID-19 outcomes

Table S4. Cumulative number and rate of hospitalizations, admissions in ICU and deaths per 100 000 during the study period.

	Hospitalizations		Admissions in ICU		Deaths	
	N	**Rate per 100000 PD**	**N**	**Rate per 100000 PD**	**N**	**Rate per 100·000 PD**
Vaccination status						
Unvaccinated	493	0·51	15	0·02	2	<0·01
Partially vaccinated	75	0·32	0	0	0	0
Fully vaccinated	59	0·24	0	0	0	0
Sex						
Male	351	0·47	9	0·01	2	<0·01
Female	276	0·39	6	0·01	0	0
Age						
5	105	0·52	1	0·00	0	0
6	82	0·41	2	0·01	0	0
7	93	0·46	3	0·01	0	0
8	88	0·43	6	0·03	0	0
9	80	0·38	0	0	0	0
10	84	0·40	2	0·01	2	0·01
11	95	0·45	1	0·00	0	0

Supplementary Material 5

Table S5. Effectiveness of BNT162b2 vaccines against laboratory-confirmed COVID-19–related with diagnosis at different time intervals after completion of the primary vaccination cycle

Vaccination status	N. infection	Person-days (PD)	Rate per 100000 PD	Crude IRR	VE (%)	VE adj (%)
Unvaccinated	562083	131065931	428.9	1	-	-
Partially vaccinated	83441	25722835	324.4	0.75	24.4	27.4 (26.4-28.4)
0-14 days fully vaccinated	29412	14626624	201.1	0.47	53.1	38.7 (37.7-39.7)
15-28 days fully vaccinated	29869	13705818	217.9	0.51	49.2	29.3 (28.1-30.4)
29-42 days fully vaccinated	29906	11633841	257.1	0.60	40.1	23.1 (21.7-24.5)
43-84 days fully vaccinated	32045	11711274	273.6	0.64	36.2	21.2 (19.7-22.7)

VE: vaccine effectiveness

Supplementary Material 6

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